PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	05 JAN 2006
Applicant's or agent's file reference 19154.005	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/25508	05 August 2004 (05.08.2004)	07 August 2003 (07.08.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 48/00 and US Cl.: 514/44

Applicant

CHIRON CORPORATION

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	12 December 2005 (12.12.2005)	Jon B. Ashen Telephone No. 703-308-1235

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/25508

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-3,5-8 and 10-25

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-3, 5-8 and 10-25	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-3, 5-8 and 10-25	NO
Industrial applicability (IA)	Claims 1-3, 5-8 and 10-25	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-3, 5-8 and 10-25 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 1-3, 5-8 and 10-25 are indefinite for the following reason(s): All of the instant claims are drawn to, "The use of" which renders the claims indefinite. However, a search of the claims in the instant application has been carried out based on the interpretation that the claims are drawn to a method of making a medicament.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-3, 5-8 and 10-25 lack an inventive step under PCT Article 33(3) as being obvious over Lillie et al., Yu et al., Bennett et al. and Bertrand et al. Lillie et al. teach a nucleic acid molecules associated with breast cancer including a nucleic acid molecule that comprises and/or overlap instant SEQ ID NO: 5 which is SEQ ID NO:465 which codes for human trefoil factor (trefoil factor 3 or TFF3) (pg. 2, line 30 to pg. 4, line 8). Lillie et al. teach a method of treating breast cancer comprising administering a pharmaceutical composition comprising antibodies targeted to the protein expressed from instantly claimed SEQ ID NO: 5 and antisense oligonucleotides that overlap SEQ ID NO: 5 to cells and patients and that their method of treatment can further comprise administration of a chemotherapeutic agent (pg. 8-11, pgs. 26-47:antibodies antisense and chemotherapeutics). The teachings of Lillie et al. of methods of treatment and the preparation of pharmaceutical compositions are considered to be inherent teachings of a method of making a medicament because in order to use the medicament in a method of treatment it must, of course, be made. Lillie et al. do not teach dsRNA for RNAi for use in making a medicament comprising an RNAi molecule. Yu et al. teach a nucleic acid molecules associated with colon cancer including a nucleic acid molecule that comprises and/or overlaps instant SEQ ID NO: 5 which is SEQ ID NO:13 which codes for human trefoil factor 3 (col. 3, figure 13). Yu et al. teach a method of treating colon cancer comprising administering a pharmaceutical composition of antisense oligonucleotides that overlap SEQ ID NO: 5 (col. 3-4; col. 16-22) and that their method of treatment can further comprise administration of other therapeutic compounds (col. 17). The teachings of Yu et al., of methods of treatment and the preparation of pharmaceutical compositions are considered to be inherent teachings of a method of making a medicament because in order to use the medicament in a method of treatment it must, of course, be made. Bennett et al. provide an extensive teaching of how to make and use antisense oligonucleotides as known in the art including an exhaustive disclosure of how to make and use antisense oligonucleotides that target and inhibit the expression of a given gene once the primary nucleotide sequence of that gene is known. Bennett et al. provide an extensive teaching of pharmaceutical compositions comprising antisense oligonucleotides and further therapeutic agents that can be chemotherapeutic agents (col. 2, line 65- col. 25, line 12). Bertrand et al. teach that siRNAs are quantitatively more efficient and the gene silencing effect is longer lasting, when compared to antisense oligonucleotides.

Therefore, the skilled artisan would not have considered, at the time the instant invention was made, that it would require an inventive step to practice a method of making a medicament comprising a trefoil factor 3 (TFF3) neutralizing agent that was an antisense oligonucleotide that comprised or overlapped SEQ ID NO: 5 because SEQ ID NO: 5, that comprises the coding sequence of TFF3, was known in the art to be overexpessed in breast and colon cancers (as taught by Lillie et al. and Yu et al.) and because methods of treating cancer comprising targeting the particular identified genes/proteins overexpressed in colon and breast cancers using antibodies or antisense wherein the antibodies or antisense were used in combination with a traditional therapy that was chemotherapy or hormone ablation therapy were known in the art (as taught by Lillie et al, Yu et al. and Bennett et al.). One of skill would also not have considered, at the time the instant invention was made, that it would require an inventive step to practice a method of making a medicament comprising a trefoil factor 3 (TFF3) neutralizing agent that was an RNAi molecule that comprised or overlapped SEQ ID NO: 5 because siRNAs were known in the art to be more effective than antisense and antisense to the particular TFF3 now claimed was taught in the prior art. A method of making a medicament for use in the treatment of cancer is also reasonably interpreted, in light of the disclosures above, to be a method of making a medicament that modulates TFF3 expression in a cell, that modulates apoptosis, that inhibits tumor growth, that modulates at least one physiological effect and that inhibits proliferation of a cell. One of skill would have been motivated and expected success in making a medicament as claimed because the prior art of Lillie et al. and Yu et al. taught the

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

differential expression of TFF3 in breast and colon cancers, thereby providing TFF3 (instantly claimed SEQ ID NO: 5), as a therapeutic target and because the prior art provides an extensive and exhaustive teaching of how to make pharmaceutical compositions comprising antisense oligonucleotides (as taught by Bennett et al.) and because RNAi molecules are more effective and efficient than antisense (as taught by Bertrand et al.).

Claims 1-3, 5-8 and 10-25 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.